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Assistant Commissioner for Patents

Washington, D.C. 20231

Elman 13 2007

TOWNSEND and TOWNSEND and CREW LLP

By: Jan Kane

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LEE et al.

Application No.: 10/028,726

Filed: December 21, 2001

For: PRODUCTS AND METHODS FOR CONTROLLING THE SUPPRESSION OF THE NEOPLASTIC PHENOTYPE

Examiner: Not yet assigned

Art Unit:

1633

COMMUNICATION UNDER

37 C.F.R. §§ 1.821-1.825

AND

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents Washington, D.C. 20231

Sir:

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, 37 C.F.R. §§ 1.821-1.825, mailed December 13, 2002, Applicants submit that the computer-readable form in the instant application is identical with that filed in Application No. 08/472,760, filed November 27,1996. In accordance with 37 C.F.R. § 1.821(e), please use the computer-readable form filed in Application No. 08/472,760 as the computer-readable form for the instant application. A paper copy of the last filed Sequence Listing from Application No. 08/472,760 is submitted herewith. The information in the paper copy of the Sequence Listing is identical to that which is in the computer readable form, as required under 37 C.F.R. § 1.821(f).

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It is understood that the Patent and Trademark Office will make the necessary changes in application number and filing date for the computer-readable form that will be used for the instant application.

Please amend the specification in adherence with 37 C.F.R. §§ 1.821-1.825 as follows.

In the Specification:

Please replace paragraph [152] beginning at page 27, line 15, with the following:

[152] --The hypothetical protein predicted from the nucleotide sequence was expected to have MW about 106 kD. The immunoprecipitated protein has a MW about 110-114 kD. The complete RB protein amino acid sequence (SEQ ID NO:2) is illustrated in Table 1. This complete sequence obtained from the newly reconstructed clone which contains the most 5' end stretch missing in the original cDNA clone Science, 235:1394-1399 (1987).

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TABLE 1

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M P P K T P R K T A A T A A A A A A E P P A P P P P P P E E D P E
                                                 34)
QDSGPEDLPLVRLEFEETEEPDFTALCQKLKIPDHVRERA
                                                 74)
WLTWEKVSSVDGVLGGYIQKKKELWGICIFIAAVDLDEMS
                                               (114)
FTFTELQKNIEISVHKFFNLLKEIDTSTKVDNAMSRLLKK
                                               (154)
YDVLFALFSKLERTCELIYLTQPSSSISTEINSALVLKVS
                                               (194)
WITFLLAKGEVLQMEDDLVISFQLNLCVLDYFIKLSPPML
                                               (234)
LKEPYKTAVIPINGSPRTPRRGQMRSARIAKQLENDTRII
                                               (274)
EVLCKEHECNIDEVKNVYFKNFIPFMNSLGLVTSNGLPEV
                                               (314)
ENLSKRYEEIYLKNKDLDARLFLDHDKTLQTDSIDSFETQ
                                               (354)
RTPRKSNLDEEVNVIPPHTPVRTVMNTIQQLMMILNSASD
                                               (394)
QPSENLISYFNNCTVNPKESILKRVKDIGYIFKEKFAKAV
                                               (434)
GQGCVEIGSQRYKLGVRLYYRVMESMLKSEEERLSIQNFS
                                               (474)
KLLNDNIFHMSLLACALEVVMATYSRSTSQNLDSGTDLSF
                                               (514)
PWILNVLNLKAFDFYKVIESFIKAEGNLTREMIKHLERCE
                                               (554)
HRIMESLAWLSDSPLFDLIKQSKDREGPTDHLESACPLNL
                                               (594)
PLQNNHTAADMYLSPVRSPKKKGSTTRVNSTANAETQATS
                                               (634)
AFQTQKPLKSTSLSLFYKKVYRLAYLRLNTLCERLLSEHP
                                               (674)
ELEHIIWTLFQHTLQNEYELMRDRHLDQIMMCSMYGICKV
                                               (714)
KNIDLKFKIIVTAYKDLPHAVQETFKRVLIKEEEYDSIIV
                                              (754)
FYNSVFMQRLKTNILQYASTRPPTLSPIPHIPRSPYKFPS
                                               (794)
SPLRIPGGNIYISPLKSPYKISEGLPTPTKMTPRSRILVS
                                               (834)
IGESFGTSEKFQKINQMVCNSDRVLKRSAEGSNPPKPLKK
                                               (874)
LRFDIEGSDEADGSKHLPGESKFQQKLAEMTSTRTRMQKQ
                                               (914)
                                               (928)
KMNDSMDTSNKEEK
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single-letter abbreviations for the amino acid residues are: A, Ala; C, Cys; D, Asp; E, Gly; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.--
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Please replace paragraph [153] beginning at page 27, line 15, with the following:

[153] --The amino acid sequence (Table 1; SEQ ID NO:2) is written in the abbreviation code recognized in the art. Single-letter abbreviations for the amino acid residues are: A = Alanine, C = Cysteine, D = Aspartic acid, E = Glutamic Acid, F = Phenylalanine, G = Glycine, H = Histidine, I = Isoleucine, K = Lysine, L = Leucine, M = Methionine, N =

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Asparagine, P = Proline, Q = Glutanine, R = Arginine, S = Serine, T = Threonine, V = Valine, W = Tryptophane and Y = Tyrosine.--

Please replace paragraph [225] beginning at page 27, line 15, with the following:

[225] --Pending U.S. patent application Serial No. 108,748 discloses and claims the RB gene and its clone. The RB gene and its clone had the nucleotide and amino acid sequences sequence depicted in <u>Table 4 Table 2 (SEQ ID NOS:1 and 2)</u>.

TABLE 4

TTCC	GGTT	TT	TCTCA	\GGGC	A CC	STTGA	LTAAL	TAT	TTTC	STAA	CGGG	AGTO	GG C	AGAC	GACGG		60
GGCG	TGCC	CCC	GCGTG	CGCC	C GC	CGTCC	TCCI	CCC	CCGGC	CGCT	CCTC	CCACA	AGC T	rcgc1	rggctc		120
CCGC	CGCC	GA	AAGGC	GTC													171
					Met	Pro	Pro	Lys	Thr	Pro	Arg	Lys	Thr		Ala		
· · · · · · · · · · · · · · · · · · ·					1				5					10			
ACC	GCC	GCC	GCT	GCC	GCC	GCG	GAA	CCC	CCG	GCA	CCG	CCG	CCG	CCG	CCC	~~	219
Thr	Ala	Ala	Ala	Ala	Ala	Ala	Glu	Pro	Pro	Ala	Pro	Pro	Pro	Pro	Pro		
	· · · · · · · · · · · · · · · · · · ·		15					20					25				
a am	a a m	a	aza			G7.G	a va	C A C	אממ	CCC	CCC	CAC	GAC	CTC	CCT		267
			GAG Glu														207
Pro	PIO	30		ASD	PIO	Giu	35	ASD	261	Gry	FIO	40	ASD.	<u> 110 u</u>			
		30		· · · · · · · · · · · · · · · · · · ·													
CTC	GTC	AĢG	CTT	GAG	TTT	GAA	GAA	ACA	GAA	GAA	CCT	GAT	TTT	ACT	GCA		315
Leu	Val	Arg	Leu	Glu	Phe	Glu	Glu	Thr	Glu	Glu	Pro	Asp	Phe	Thr	Ala		
	45					50					55						
ጥጥል	ጥርጥ	CAG	מממ !	מידים	AAG	ΔΤΔ	CCA	GAT	САТ	GTC	AGA	GAG	AGA	GCT	TGG	•	363
			Lys														
60	Cyb	<u> </u>	<u> </u>		<u>-75</u> 65					70					75		
			 · : · · · · · · · · · · · · · · · · · 														
TTA	ACT	TGG	GAĢ	AAA	GTT	TÇA	TCT	GTG	GAT	GGA	GTA	TTG	GGA	GGT	TAT		411
Leu	Thr	Trp	Glu	Lys	Val	Ser	Ser	Val	Asp	Gly	Val	Leu	Gly	Gly	Tyr		
				80					85				<u>.</u>	90			
													3 mm	aar	G G 7		450
ATT	CAA	AAG	AAA	AAG	GAA	.CTG	TGG	GGA	ATC	TGT	ATC	TTT	ATT	GCA	GCA 37.5		459
Ile	Gln	Lys	Lys	Lys	Glu	Leu	Trp		lle	Cys	тте	Pne		Ala	Ala		
			95					100				<u> </u>	105				
GTT	GAC	CTA	A GAT	GAG	ATG	TCG	TTC	ACT	TTT	ACT	GAG	CTA	CAG	AAA	AAC		507
Val	Asp	Leu	ı Asp	Glu	Met	Ser	Phe	Thr	Phe	Thr	Glu	Leu	Gln	Lys	Asn	-	
		110					115					120					•
		-							•						•		•

PATENT LEE et al. Application No.: 10/028,726 Page 5 ATA GAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr GAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser GCA TTG GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GGG Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly GAA GTA TTA CAA ATG GAA GAT GAT CTG GTG ATT TCA TTT CAG TTA ATG Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu AAA GAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA CCT CGA Lys Glu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg ACA CCC AGG CGA GGT CAG AAC AGG AGT GCA CGG ATA GCA AAA CAA CTA Thr Pro Arg Arg Gly Gln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu GAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe ATG AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu

PATENT LEE et al. Application No.: 10/028,726 Page 6 GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser ATA GAC AGT TTT GAA ACA CAG AGA ACA CCA CGA AAA AGT AAC CTT GAT Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp GAA GAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG Glu Glu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA GGA TAC ATC TTT AAA Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys GAG AAA TTT GCT AAA GCT GTG GGA CAG GGT TGT GTC GAA ATT GGA TCA Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA TCC Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser ATG CTT AAA TCA GAA GAA GAA CGA TTA TCC ATT CAA AAT TTT AGC AAA Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA Ser Gly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA GCA GAA Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu

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GGC	AAC	TTG	ACA	AGA	GAA	ATG	АТА	ΑΑΑ	САТ	тта	GAA	CGA	TGT	GAA	CAT	1803
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		ATG			CTT	GCA		CTC		GAT	TCA	· ·	TTA	TTT	GAT	1851
Arg	Ile	Met	GIu	560	Leu	Ala	Trp	Leu	565	Asp	Ser	Pro	ьeu	570	Asp	
				360					303		_,		· · · · · ·	370		
CTT	ATT	AAA	CAA	TCA	AAG	GAC	CGA	GAA	GGA	CCA	ACT	GAT	CAC	CTT	GAA	1899
Leu	Ile	Lys	Gln	Ser	Lys	Asp	Arg	Glu	Gly	Pro	Thr	Asp	His	Leu	Glu	
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SEL	Ala	590	PLO	пец	MOII	пси	595	пси	0111	Abii	, ADII	600	<u> </u>	2114	1114	
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GAT	ATG	TAT	CTT	TCT	CCT	GTA	AGA	TCT	CCA	AAG	AAA	AAA	GGT	TCA	ACT	1995
Asp	Met	Tyr	Leu	Ser	Pro	Val	Arg	Ser	Pro	Lys		Lys	Gly	Ser	Thr	
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7.00	CCT	CTA	አለጥ	Tr CTT	አ ርጥ	CCA	<u>አ</u> አጥ	CCA	GAG	ΔCΔ	$C\Delta\Delta$	GCA	ACC	тса	GCC	2043
ACG Thr		- <u> </u>	_							• •		Ala				2013
620	7119	<u> </u>	71011		625	1120				630					635	
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									ACC				CTG	TTT	TAT	2091
Phe	Gln	Thr	Gln		Pro	Leu	Lys	Ser	-	Ser	Leu	Ser	Leu		Tyr	
				640	x. <u>u</u> r				645	····			•	650		
2	Z Z Z	GTG	ירביד	CGG	СТА	GCC	ТАТ	СТС	CGG	CTA	AAT	ACA	CTT	$\mathbf{T}\mathbf{G}^{^{\downarrow}}\mathbf{T}$	GAA	2139
											,	Thr			Glu	
	,		655					660					665			
	CTT														CTT	2187
Arg	Leu	• • • • • • • • • • • • • • • • • • • •	Ser	Glu	His	Pro	675	ьеи	Glu	HIS	TTE	1le 680	Trp	THE	ьей	
		670					6/5				×					
TTC	CAG	CAC	ACC	CTG	CAG	AAT	GAG	TAT	GAA	CTC	ATG	AGA	GAC	AGG	CAT	2235
															His	
	685			· - · · · · · · · · · · · · · · · · · ·		690				_	695					
		~			7 070	man		7 M.C	m 2 m	aaa	7 CT 7	maa	7N 7N 7N	CITIC!	7 7 C	2283
				ATG			TCC								AAG Lys	2283
700	Asp	GIII	TIE	Mec	705	Cys	Ser	Met		710	110	Суб	LLY S		715	
700					705							,	•		· · · · · · · · · · · · · · · · · · ·	
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Asn	Ile	Asp	Leu	Lys	Phe	Lys	Ile	Ile			Ala	Tyr	Lys		Leu	
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110	1110		735					740					745		<u> </u>	
GAG	TAT	GAT	TCT	ATT	ATA	GTA	TTC	TAT	AAC	TCG	GTC	TTC	ATG	CAG	AGA	2427
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PATENT LEE et al. Application No.: 10/028,726 Page 8 Glu Tyr Asp Ser Ile Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg CTG AAA ACA AAT ATT TTG CAG TAT GCT TCC ACC AGG CCC CCT ACC TTG Leu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu TCA CCA ATA CCT CAC ATT CCT CGA AGC CCT TAC AAG TTT CCT AGT TCA Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser CCC TTA CGG ATT CCT GGA GGG AAC ATC TAT ATT TCA CCC CTG AAG AGT Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA - 2907 Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT Asn Lys Glu Glu Lys

GGATTCATTG TCTCTCACAG ATGTGACTGT AT

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PATENT

TABLE 4

GCCGTGCCCC GCGTCCGCCC GCGTCCTCCT CCCCGGGCCT CCCTCCACACC TCGCTCGCTC CCCCCGCCCCA AAGCCCTC ATC CCC CCC AAA ACC CCC CGA AAA ACG CCC GCC Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala 1 5 10 ACC CCC CCC CCT GCC CCC GCC GCA CCC CCG CCC CCC CCC CCC					
Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala 1 1 5 10 Acc GCC GCC GCC GCC GCC GCC GCC GCC GCC G	TTCCGCTTTT TCT	CAGCCCA CGTTG	AATT ATTTTGT	AA CGGGAGTCGG GAGAGGACGG	60
Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala 1 5 10 Acc GCC GCC GCC GCC GCC GCAA CCC GCG GCA CCC CCC	CCCTCCCC CCC	TGCGCGC GCGTC	STECT CCCCCCC	CT CCTCCACAGC TCCCTCGCTC	120
Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala 1 5 10 Acc Gcc Gcc Gcc Gcc Gcc Gca Gcc Gcc Gcc G					171
ACC GCC GCT GCC GCC GCC GAA CCC CCG GCA CCC CCG CCG					
Acc ccc ccc ccc ccc ccc ccc ccc ccc ccc	***	- Met Pro	-Pro Lys Thr P	ro Arg Lys Inr Ala Ala	
The Ala Ala Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro 15 20 25 CCT CCC TAC GAC GAC CCA GAC CAG GAC AGC GCC CCC GAG GAC CTC CCT Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro 30 35 40 CTC CTC AGC CTT GAC TTT GAA GAA ACA GAA GCT GAT TTT ACT GCA 45 50 55 TTA TGT CAC AAA TTA AAG ATA CCA GAT CAT GTC AGA AGA AGA GCT TGC GCT GCT GAC GAT TTA AGA ATA CCA GAT CAT GTC AGA GAG AGA GCT TGC GCT ACC GAT ATA AGA ATA CCA GAT CAT GTC AGA GAG AGA GCT TGC GCT GCT GCT GCT GCT GCT GCT GCT		1		10	
The Ala Ala Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro 15 20 25 CCT CCC TAC GAC GAC CCA GAC CAG GAC AGC GCC CCC GAG GAC CTC CCT Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro 30 35 40 CTC CTC AGC CTT GAC TTT GAA GAA ACA GAA GCT GAT TTT ACT GCA 45 50 55 TTA TGT CAC AAA TTA AAG ATA CCA GAT CAT GTC AGA AGA AGA GCT TGC GCT GCT GAC GAT TTA AGA ATA CCA GAT CAT GTC AGA GAG AGA GCT TGC GCT ACC GAT ATA AGA ATA CCA GAT CAT GTC AGA GAG AGA GCT TGC GCT GCT GCT GCT GCT GCT GCT GCT	ACC GCC GCC GC	T-GCC GCC GCG	GAA CCC CCG G	CA CCG CCG CCG CCC	219
CCT CCG TAG CAG CAC CCA GAG CAG CAG GAC GCC CCG GAG GA					
CCT CCG TAG GAG GAC CCA GAG CAG GAC AGC GGC CCG GAG CAC CTG CCT Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro 30 35 40 CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA CAA CCT GAT TTT ACT GCA Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala 45 50 55 TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG Leu Cys Gln Lys Leu Lys He Pro Asp His Val Arg Glu Arg Ala Trp 60 65 70 75 TTA ACT TGG GAG AAA GTT TCA TCT GTC GAT GCA GTA TTG GGA GGT TAT Leu Thr Trp Glu Lys Val Ser Ser Val Asp Gly Val Leu Cly Gly Tyr 80 85 90 ATT CAA AAG AAA AAG GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA He Gln Lys Lys Glu Leu Trp Gly He Cys He Phe He Ala Ala 100 105 CTT GAC CTA GAT GAG ATG TCC TTC ACT TTT ACT GAG CAA AAC ST Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Gln Lys Asn 110 115 120 ATA CAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT 11e Glu He Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu He Asp 125 130 135 ACC AGT ACC AAA GTT GAT AAT GCT ATC TGA AGA CTC TTG AAG AAG TAT Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr 140 145 150 156					
Pro Clu Clu Asp Pro Clu Cln Asp Ser Cly Pro Clu Asp Leu Pro 30 35 40 CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA Leu Val Arg Leu Clu Phe Glu Clu Thr Clu Clu Pro Asp Phe Thr Ala 45 50 TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA CAG AGA GCT TGG Leu Cys Cln Lys Leu Lys Ile Pro Asp His Val Arg Clu Arg Ala Trp 60 65 TTA ACT TGG GAG AAA GTT TCA TCT GTG CAT GGA GTA TTG GGA GGT TAT Leu Thr Trp Clu Lys Val Ser Ser Val Asp Gly Val Leu Cly Cly Tyr 80 ATT CAA AAG AAA AAG GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA Ile Cln Lys Lys Clu Leu Trp Gly Ile Cys Ile Phe Ile Ala Ala 95 CTT GAC CTA GAT GAG ATC TCG TTC ACT TTT ACT GAG CTA CAG AAA AAC Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Cln Lys Asn 110 ATA GAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT Ile Clu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Clu Ile Asp 125 ACC ACT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr 140 CAT CTA TTG TTT GCA CTC TTC ACC ATA TTG GAA ACG ACA TCT GAA CTT			. —	•	
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140 145 150 155 CAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT 6					
CAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG AGA TGT GAA CTT 6	inr ber inr b	in vai mul mul	I MIA TICC DCI	150 155	
	140	145		TO 0 TO 0	
		דיים מביא מיים יי ים	<u>. አርር አአአ ጥጥር (</u>	CAA ACC ACA TOT CAA CTT	65
					, 3 - 2
	Asp val Leu Pr				

PATENT LEE et al. Application No.: 10/028,726 Page 10 ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser 175 180 185 GCA TTG GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GCG Ala Leu Val Leu Lys Val Ser Trp-Ile Thr Phe Leu Leu Ala Lys Gly ______190 _________195 ______200 GAA GTA TTA CAA ATG GAA GAT GAT CTG GTG ATT TCA TTT CAG TTA ATG Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met $\frac{205}{}$ $\frac{210}{}$ $\frac{215}{}$ CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTC CTC Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu 220 225 230 235 AAA CAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA CCT CGA Lys Clu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Cly Ser Pro Arg 240 245 250 ACA CCC AGG CGA GGT CAG AAC AGG AGT GCA CGG ATA GCA AAA CAA CTA Thr Pro Arg Arg Cly Cln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu ______255 ______260 ____265 GAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys AAT ATA CAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe 285 290 295 ATG AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA 1083 Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu 300 315 315 AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu 320 325 330 GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser 335 340 345 ATA CAC ACT TTT CAA ACA CAG AGA ACA CCA CGA AAA ACT AAC CTT GAT -1227Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp 355 360 CAA CAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG ----- 1275 Glu Glu Val Asn Val Ile Pro Pro His Thr Pro Val Arg Thr Val Met 365 370 375

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AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA	- 1323
Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln 380 395	
380 385 385 390 390	
CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA	1371
Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro	
400 405	
AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA GGA TAC ATC TTT AAA	- 1419
Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys	
415 420 425	
GAG AAA TTT GCT AAA GCT GTG GGA CAG GGT TGT GTC GAA ATT GGA TCA	1467
Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser	
435 440	
CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA-TCC	1515
Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser	
<u>445</u> <u>450</u> <u>455</u>	
ATG CTT AAA TCA GAA GAA GAA CGA TTA TCC ATT CAA AAT TTT AGC AAA	1563
Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys	
460 475 475	
CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT	- 1611
Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu	
480485490	
GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT	1659
Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp	•
TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA	1707
Ser Gly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu	
<u>510</u> 515 520	
AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA GCA GAA	1755
Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu	
$\frac{525}{530} = \frac{535}{530}$	
	- 1803
GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT GAA CAT Gly Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Glu His	
540 545 555 550 555	
	1851
CCA ATC ATG GAA TCC CTT CCA TGG CTC TCA GAT TCA CCT TTA TTT GAT	1831
Arg Ile Met Glu Ser Leu Ala-Trp Leu Ser Asp Ser Pro Leu Phe Asp	
CTT ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC CTT GAA	
Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu	

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LEE et al. Application No.: 10/028,726 Page 12	5 .				PATEN
TCT GCT TGT CCT CTT AAT	CTT CCT	CTC CAG AA	T AAT CAC ACT	GCA GCA	1947
Ser Ala Cys Pro Leu Ası	n Leu Pro I	Leu Gln As	n Asn His Thi	Ala Ala	
590	595				
GAT ATC TAT CTT TCT CC	г СТА <u>АСА .</u>	 Р <u>СТ ССА АА</u>	C AAA AAA CCT	TCA ACT	- 1995
Asp Met Tyr Leu Ser Pro					
- 605	$\frac{610}{}$		615		
·					_
ACG CGT GTA AAT TCT AC	r GCA AAT (SCA GAC AC	A CAA GCA AC(TCA GCC	2043
Thr Arg Val Asn Ser Th	r Ala Asn i	Ala Glu Th	r Gln Ala T hi	Ser Ala	
620 62	5	63	0		
TTC CAG ACC CAG AAG CC	አ <u>ጥጥር አአአ '</u>	TOT ACC TO	T CTT TCA CT (TAT TAT	2091
Phe Gln Thr Gln Lys Pr	o Leu Lys	Ser-Thr Se	r Leu Ser Lei	ı -Phe-Tyr	
		645		— 650	
AAA AAA GTG TAT CCG CT	A GCC TAT	CTC CGG CT	'A AAT ACA CT'	r TGT GAA	2139
Lys Lys Val Tyr Arg Le	u Ala Tyr	Leu Arg Le	u Asn Thr Le		•
655		660	66	-	
CCC CTT CTC TCT GAC CA	G GGA GAA		ም አጥሮ አጥሮ <u>ጥር</u>	C ACC CTT	2187
Arg Leu Leu Ser Glu Hi	c CCA GAA	IIA GAA C Iou Clu Hi	s Ile Ile Tr	o Thr Leu	210.
670	675		680		
	V .5				
TTC CAG CAC ACC CTG CA	G AAT GAG	TAT CAA CI	C ATC AGA CA	C AGG CAT	- 2235
Phe Gln His Thr-Leu Gl	n Asn Glu	Tyr Clu Lo	u Met Arg As	p Arg His	
	690		- 695		
TTC GAC CAA ATT ATG AT	o mam maa	AUC UNT CC	ነር አ ጥ አ ጥርር አአ	A CTC AAC	2283
Leu Asp Gln Ile Met Me	t Cur Ser	Mot Tyr C	v Ile Cvs Iv	s Val Lvs	2202
Leu Asp Gin 11e Met Me	E Cys DCI		0	715	
700	.5				
AAT ATA CAC CTT AAA TT	C AAA ATC	ATT GTA A	CA CCA TAC AA	G GAT CTT	2331
Asn Ile Asp Leu Lys Ph	e Lys Ile	Ile Val T	ır Ala Tyr Ly	s Asp Leu	
720		725		730	
	~	777 CCT C	ሆው መ ሞሪ አሞሪ እሽ	A CAA CAC	2379 .
CCT CAT CCT GTT CAG GF	Whr Pho	IVO Arg V	l leu lle Lv	a Clu Clu	2373
735	u me	740		5	
	·	, 10			
CAG TAT CAT TCT ATT AT	A CTA TTC	TAT AAC T	CG GTC TTC AT	G CAG AGA	-2427
Glu Tyr Asp Ser Ile Il	e Val Phe	Tyr Asn S	er Val Phe Me	t Cln Arg	
75 0	75 5		760		
		dam maa m	aa waa aaa ac	T ACC TTC	2475
CTC AAA ACA AAT ATT T	FG CAC TAT	Ala Car T	hr Ara Pro Pr	o Thr Leu	2213
Leu Lys Thr Asn Ile Lo	<u>770</u>	mid bei i	775	J 1111 1100	
	7,0				
TCA CCA ATA CCT CAC A	TT CCT CGA	AGC CCT T	AC AAG TTT CO	T AGT TCA	2523
Ser Pro Ile Pro His I	le Pro Arq	Ser Pro T	yr Lys Phe Pi	o Ser Ser	
780 7	85	7	90	795	

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CCC TTA CCG ATT CCT CGA CCG AAC ATC TAT ATT TCA CCC CTG AAG ACT Pro Leu Arg Ile Pro Cly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser 800 810	2571
CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA ACA AAA ATG ACT CCA Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro 815 820 825	2619
AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu 830 835 840	 2667
AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu 850 855	 2715
AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu 860 875	2763
CCC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu 880 885 890	- 2811
CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr 895 900 905	- 2859
CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser 910 915	2907
AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT — Asn Lys Glu Glu Lys ——925	2962
GGATTCATTG TCTCTCACAG ATGTGACTGT AT	2994

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 10, at the end of the application.

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In the Claims:

Please amend claims 35, 39 and 40 as follows:

1. (Original) A method of controlling cancer suppression in a mammal having a cancer suppressing gene, comprising the steps of:

making a substantially duplicated genetic material corresponding to the genetic material of said gene, the substantially duplicated material selected from the group consisting of a cloned cancer suppressing gene, a modified or defective cancer suppressing gene, homologues thereof, fragments thereof, and mixtures thereof; and

interchanging said duplicated genetic material and the cancer suppressing gene of the mammal.

- 2. (Original) A method of claim 1, wherein before said making a substantially duplicated genetic material, determining the chromosomal location of said cancer suppressing gene of the mammal.
- 3. (Original) A method of claim 1, wherein after said making a substantially duplicated genetic material, detecting the presence or absence of an inactive cancer suppressing gene of a tissue sample of the mammal to determine whether or not the tissue sample cancer suppressing gene is defective or absent.
- 4. (Original) A method of claim 3, wherein in response to a determination that the tissue sample cancer suppressing gene is either defective or absent, replacing a cancer suppressing gene of the mammal with its clone.

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- 5. (Original) A method of claim 3, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by measuring the amount of protein product of said cancer suppressing gene, of the tissue sample, bound by an antibody specific for said protein.
- 6. (Original) A method of claim 5, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by:
 - (a) labeling said tissue sample with radioactive isotope;
 - (b) lysing the labeled tissue;
- (c) reacting the protein product of said cancer suppressing gene with an antibody specific for said protein thereby forming a protein/antibody immunocomplex;
 - (d) autoradiographing the immunocomplex obtained in step (c); and
- (e) determining the presence or absence of the protein product by comparing the autoradiogram of step (d) with the autoradiogram of the standard protein product.
- 7. (Original) The method of claim 5, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by enzyme immunoassay techniques.
- 8. (Original) The method of claim 5, wherein the determination of whether or not the tissue sample cancer suppressing gene is defective or absent is accomplished by immunocytochemistry methods.
- 9. (Original) The method of claim 5, wherein the cancer suppressing gene is the RB gene and the protein product is ppRB¹¹⁰.

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- 10. (Original) The method of claim 1, wherein said cancer suppressing gene is replaced with substantially duplicated material selected from the group consisting of said cloned cancer suppressing gene, homologues thereof, fragments thereof, and mixtures thereof, for therapeutic purposes.
- 11. (Original) The method of claim 1, wherein said cancer suppressing gene is replaced with substantially duplicated material selected from the group consisting of said defective cancer suppressing gene, homologues thereof, fragments thereof, and mixtures thereof, for facilitating the testing of the carcinogenicity of environmental influences.
- 12. (Original) The method of claim 2, wherein the location of said cancer suppressing gene is determined by chromosome walking.
- 13. (Original) The method of claim 2, wherein the location of said cancer suppressing gene is determined through organic markers.
 - 14. (Original) A method of claim 2, wherein:

said chromosomal location of said cancer suppressing gene is determined by testing genes of a chromosome for phenotypic expression;

determining one of the genes of said chromosome to be a marker gene; and using chromosomal walking techniques to locate a cancer suppressing gene.

15. (Original) An animal genetically altered so as to have the allele of at least one cancer suppressing gene selected from the group consisting of a defective allele, a homologue thereof, a fragment thereof, and a mixture thereof.

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16. (Original) An animal of claim 15, wherein said defective allele is selected from the group consisting of defective alleles of RB genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homolgues thereof, fragments thereof, and mixtures thereof.

- 17. (Original) An animal of claim 15, wherein said allele contains a DNA fragment having at least one defective nucleotide sequence.
- 18. (Original) An animal of claim 15, wherein said defective allele contains a DNA fragment having at least one defective RB nucleotide sequence.
 - 19. (Original) The animal of claim 15, wherein said animal is a mouse.
- 20. (Original) A method for determining the carcinogenicity of suspected environmental influences, using the animal of claim 14, comprising the steps of: exposing said animal to a suspected environmental influence; observing the animal for the phenotypic expression of cancer; and determining carcinogenicity of the suspected environmental influence in response to observing a phenotypic expression of cancer in the animal.
- 21. (Original) A method of claim 20, wherein said exposing includes exposing to a source of radiation.
- 22. (Original) A method of claim 20, wherein said exposing includes exposing to tobacco combustion products.

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23. (Original) A method of claim 20, wherein said exposing includes exposing to food additives.

- 24. (Original) A method of claim 20, wherein said exposing includes exposing to artificial substances.
- 25. (Original) A method of claim 20, wherein said observing includes examining the animal for tumor development.
- 26. (Original) A method of claim 25, wherein in response to the formation of a tumor in the animal, analyzing the tumor for the presence of cancer cells.
- 27. (Original) A method of making the animal of claim 15, comprising: using at least one allele of an animal cancer suppressing gene selected from the group consisting of a defective allele, a homologue thereof, a fragment thereof, and a mixture thereof;

mutating at least one animal cell with said allele to form a mutated cell; introducing said mutated cell into an animal blastocyst;

permitting growth of the blastocyst for a given period of time sufficient to incorporate said allele into its cells; repressing genetic recombinations within said cells; transferring the blastocyst containing said allele into the uterus of a pseudo pregnant animal for giving birth subsequently to an animal bearing said allele;

breeding said animal to reproduce additional animals; and selecting the animal of claim 14 from said additional animals by determining the presence therein of the said allele.

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28. (Original) A method of claim 27, wherein before introducing said allele, removing said blastocyst from a super ovulated animal, and wherein said blastocyst is comprised of undifferentiated cells.

- 29. (Original) A method of claim 27, wherein said introducing is performed in vitro.
- 30. (Original) A pharmaceutical composition wherein the active ingredient is selected from the group consisting of a naturally occurring intact cancer suppressing gene, a cloned intact cancer suppressing gene, fragments thereof, homolgues thereof and mixtures thereof.
- 31. (Original) A pharmaceutical composition of claim 30, wherein said naturally occurring and cloned cancer suppressing gene is selected from the group consisting of RB genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homolgues thereof, fragments thereof, and mixtures thereof.
- 32. (Original) A pharmaceutical composition of claim 30, wherein the active ingredient is selected from the group consisting of RB cDNA, modified RB cDNA fragment, clones thereof, homolgues thereof and mixtures thereof.
- 33. (Original) A pharmaceutical composition of claim 31, wherein the active ingredient for each of said gene is selected from the group consisting od cDNA of said gene, fragments of said cDNA, homologues thereof and mixtures thereof.

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- 34. (Original) A pharmaceutical composition of claim 32, wherein the cancer suppressing gene is isolated from human chromosome 13 region 13q14.
- 35. (Currently amended) A pharmaceutical composition of claim 31, wherein the cancer suppressing gene and its clone each has the following nucleotide sequence comprising SEQ ID NO:1.÷

TTCCGGTTTT TCTCAGGGGA CGTTGAAATT ATTTTTGTAA CGGGAGTCGG GAGAGGACGG	60
GGCGTGCCCC GCGTGCGCGC GCGTCGTCCT CCCCGGCGCT CCTCCACAGC TCGCTGGCTC	- 120
CCGCCGCGA AAGGCGTC ATG CCG CCC AAA ACC CCC CGA AAA ACG GCC GCC	171
ACC GCC GCC GCC GCC GCG GAA CCC CCG GCA CCG CCG	219
CCT CCG TAG GAC GAC CCA GAG CAG GAC AGC GGC CCG GAG GA	267
CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA Leu Val-Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala ———————————————————————————————————	- 315
TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGC Leu Cys Gln Lys Leu Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp 65 75	- 363
TTA-ACT TGG GAG AAA GTT TCA TCT GTG GAT GGA GTA TTG GGA GGT TAT Leu Thr Trp Glu Lys Val Ser Ser Val Asp Gly Val Leu Gly Gly Tyr 80 85	411
ATT CAA AAG AAA AAG GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA Ile Gln Lys Lys Lys Glu Leu Trp Gly Ile Cys Ile Phe Ile Ala Ala 95 100 105	——4 59
GTT GAC CTA GAT GAG ATG TCG TTC ACT TTT ACT GAG CTA CAG AAA AAC Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Gln Lys Asn 110 115	507
ATA GAA ATC ACT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp 125 130 135	555

PATENT LEE et al. Application No.: 10/028,726 Page 21 ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Lys Lys Tyr 140 - 145 - 150 - 155 GAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT Asp Val Leu-Phe Ala-Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT Ile Tyr Leu Thr Cln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser CCA TTG CTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GGG-Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly GAA CTA TTA CAA ATC CAA CAT GAT CTG GTG ATT TCA TTT CAG TTA ATG Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC Leu-Cys Val-Leu-Asp Tyr-Phe Ile Lys Leu Ser Pro Pro Met Leu-Leu 220 235 230 235 AAA GAA CCA TAT AAA ACA GCT GTT ATA CCC ATT AAT GGT TCA CCT CCA Lys Glu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg ______240______245_______250 ACA CCC AGG CGA GGT CAG AAC AGG AGT GCA CGG ATA GCA AAA CAA CTA Thr Pro Arg Arg Gly Cln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu CAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT --- 987 Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His-Glu Cys 275 - AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe _____285_______ ATC AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA Met Asn Ser Leu Cly Leu Val Thr Ser Asn Cly Leu Pro Clu Val Clu 300 310 315 AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA -- 1131 Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu 320 325 330 GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT 1179 Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser

335 - 340 - 345

LEE et al. **PATENT** Application No.: 10/028,726 Page 22 ATA CAC ACT TTT CAA ACA CAC AGA ACA CCA CGA AAA ACT AAC CTT GAT Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp -350 --- 355 --- 360 GAA GAG GTG AAT GTA ATT CCT CCA CAC ACT CCA GTT AGG ACT GTT ATG Glu Clu Val Asn Val Ile Pro Pro His Thr Pro Val Arq Thr Val Met -365 -370 -375AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT TCA GCA AGT GAT CAA -- 1323 Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln 380 --- 395 --- 395 CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC TGC ACA GTG AAT CCA 1371 Pro Ser Clu Asn Leu-Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro 400 405 410 AAA GAA AGT ATA CTG AAA AGA GTG AAG GAT ATA CGA TAC ATC TTT AAA 1419 Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys <u>415</u> <u>420</u> <u>425</u> GAG AAA TTT GCT AAA GCT GTG GGA CAG GGT TGT GTC GAA ATT GGA TCA Clu Lys Phe Ala Lys Ala Val Cly Cln Cly Cys Val Clu Ile Cly Ser _____430______435______440 CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC CGA GTA ATG GAA TCC Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser ___45_____450 ATG CTT AAA TCA GAA CAA CAA CGA TTA TCC ATT CAA AAT TTT AGC AAA 1563 Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA TTG GCG TGC GCT CTT ---1611 Leu-Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu CAC GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA TCT CAG AAT CTT GAT Glu Val Val-Met Ala Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp 495 500 505 TCT GGA ACA GAT TTG TCT TTC CCA TGG ATT CTG AAT GTG CTT AAT TTA 1707 Ser Cly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu <u>510</u> <u>520</u> AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT TTT ATC AAA GCA GAA Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu <u> 525 - 535 </u> GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA GAA CGA TGT GAA CAT Gly Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Glu His

540 --- 545 --- 550 ---

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CGA ATC ATG GAA TCC CTT GCA TGG CTC TCA GAT TCA CCT TTA TTT GAT	1851
Arg Ile Met Clu Ser Leu Ala Trp Leu Ser Asp Ser Pro-Leu Phe Asp 560 570	•
CTT-ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC CTT GAA	1899
Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu 575 580 585	· · · · · · · · · · · · · · · · · · ·
TCT CCT TGT CCT CTT AAT CTT CCT CTC CAG AAT AAT CAC ACT GCA GCA	1947
Ser Ala Cys Pro Leu Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala 590 595 600	
CAT ATC TAT CTT TCT CCT GTA ACA TCT CCA AAC AAA AAA GGT TCA ACT	1995
Asp Met Tyr Leu Ser Pro Val Arg Ser Pro Lys Lys Cly Ser Thr	
ACG CGT GTA AAT TCT ACT CCA AAT GCA GAG ACA CAA GCA ACC TCA GCC	2043
Thr Arg Val Asn Ser Thr Ala Asn Ala Clu Thr Cln Ala Thr Ser Ala 620 635	
TTC CAG ACC CAG AAG CCA TTG AAA TCT ACC TCT CTT TCA CTG TTT TAT	2091
Phe-Gln Thr Gln Lys Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe-Tyr 640 650	
AAA AAA CTG TAT CGG CTA GCC TAT CTC CGG CTA AAT ACA CTT TGT GAA	- 2139
Lys Lys Val Tyr Arg Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu 655 660 665	
CCC CTT CTC TCT GAG CAC CCA GAA TTA GAA CAT ATC ATC TGG ACC CTT	- 2187
Arg Leu Leu Ser Glu His Pro Glu Leu Glu His Ile Ile Trp-Thr-Leu 670 675 680	
TTC CAG CAC ACC CTG CAG AAT GAG TAT GAA CTC ATG AGA GAC AGG CAT	- 2235
Phe Gln His Thr Leu Gln-Asn Glu-Tyr-Glu Leu Met Arg Asp Arg-His 685 695	
TTG GAC CAA ATT ATG ATG TGT TCC ATG TAT GGC ATA TGC AAA GTG AAG	2283
Leu Asp Cln Ile Met Met Cys Ser Met Tyr Cly Ile Cys Lys Val Lys 700 715 715	
AAT ATA GAC CTT AAA TTC AAA ATC ATT GTA ACA GCA TAC AAG GAT CTT	2331
Asn Ile Asp Leu Lys Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu 720 725 730	
CCT CAT GCT GTT CAG GAG ACA TTC AAA CGT GTT TTG ATC AAA GAA GAG	2379
Pro His Ala Val Gln Glu Thr Phe Lys Arg Val Leu Ile Lys Glu Glu	
GAG TAT GAT TCT ATT ATA GTA TTC TAT AAC TCG GTC TTC ATG CAG AGA Glu Tyr Asp Ser Ile Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg	2427

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Page 24		
CTG AAA ACA AAT ATT TTG CAG TAT CCT TCC ACC AGG CCC CCT A	CC TTC	2475
Leu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro T		. 4 - 7 4
765 770 775		
TCA CCA ATA CCT CAC ATT CCT CGA ACC CCT TAC AAG TTT CCT A		2523
Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro S		
780 785 790	 795	
CCC TTA CGG ATT CCT GGA GGG AAC ATC TAT ATT TCA CCC CTG A	AC ACT	- 2571
Pro Leu Arg Ile Pro Cly Cly Asn Ile Tyr Ile Ser Pro Leu L	ys Ser	
	10	
CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG A	CT-CCA	- 2619
Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met T	hr Pro	
815 820 825		,
AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT T	CT GAG	- 2667
Arg Ser Arg Ile Leu Val Ser Ile Cly Clu Ser Phe Cly Thr S		
——————————————————————————————————————		
	Ima ama	2715
AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT C		
Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg V 	ar bea	
AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTC AAA A	<u> </u>	2763
Lys Arg Ser Ala Clu Cly Ser Asn Pro Pro Lys Pro Leu Lys I		2705
860 - 865 870	875	
000	3,3	
CCC TTT GAT ATT CAA CCA TCA GAT GAA GCA GAT GGA AGT AAA C	AT CTC	- 2811
Arg Phe Asp Ile Clu Gly Ser Asp Glu Ala Asp Gly Ser Lys H	l is-Leu	
880 885 8	190	
CCA CGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT T	CT ACT	2859
Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr S		·
CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT A	CC TCA	2907
Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp T	Thr Ser	
910 915 920		
AAC AAC CAA CAC AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTAG	CACCTCT	2962
Asn-Lys-Glu-Glu-Lys	<i>:</i>	· :
925		
GGATTCATTG TCTCTCACAG ATGTGACTGT AT		2994
	•	

36. (Original) A pharmaceutical composition of claim 32, wherein said RB cDNA fragment is selected from the group consisting of RB-1, RB-2, RB-5, y79R8 and mixtures thereof.

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- 37. (Original) A pharmaceutical composition of claim 32, wherein a resulting mRNA transcript of said RB cDNA fragment has 4.6 kb.
- 38. (Original) A pharmaceutical composition of claim 37, wherein the cloned genomic DNA has at least 27 exons.
- 39. (Currently amended) A pharmaceutical composition of claim 30, wherein the cloned RB cDNA transcribes into mRNA which translates in protein having an amino acid sequence comprising SEQ ID NO:2.÷

KLLNDNIFHMSLLACALEVVMATYSRSTSQNLDSCTDLSF (514)(554)PWILNVLNLKAFDFYKVIESFIKAECNLTREMIKHLERCE HRIMESLAWLSDSPLFDLIKQSKDREGPTDHLESACPLNL (-5.9.4)PLONNHTAADMYLSPVRSPKKKCSTTRVNSTANAETQATS (634) (674)AFOTOKPLKSTSLSLFYKKVYRLAYLRLNTLCERLLSEHP (-7.1.4)ELEHIIWTLFOHTLONEYELMRDRHLDQIMMCSMYGICKV (754)KNIDLKFKIIVTAYKDLPHAVOETFKRVLIKEEEYDSIIV FYNSVFMORLKTNILQYASTRPPTLSPIPHIPRSPYKFPS (794)(834)SPLRIPGGNIYISPLKSPYKISEGLPTPTKMTPRSRILVS **ICESFCTSEKFQKINQMVCNSDRVLKRSAEGSNPPKPLKK** (874)**LRFDIEGSDEADGSKHLPGESKFQQKLAEMTSTRTRMQKQ** (914)(928)-KMNDSMDTSNKEEK-

single letter abbreviations for the amino acid residues are:
A, Ala; C, Cys; D, Asp; E, Cly; F, Phe; G, Gly; H, His;

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I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

40. (Currently amended) A DNA nucleotide sequence comprising SEQ

ID NO:1.÷

TTCCCCTTTT TCTCACCCCA CCTTGAAATT ATTTTTGTAA CGCGAGTCCC GAGACGACCC	60
GGCGTGCCCC GCGTCCGCCTCCT CCCCGGCGCT-CCTCCACAGC TCGCTGGCTC	120
CCCCCCCA AACCCCTC ATC CCC CCC AAA ACC CCC C	171
	•
ACC CCC CCC CCC CCC CCC CCC CCC CCC CCC	219
Thr Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro	
25	
CCT CCG TAG GAG GAG CCA GAG GAG GAG GAG GAG GAG CTG CCT	267
Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro	
30	
CTC GTC ACC CTT CAC TTT GAA GAA ACA GAA CAA CCT GAT TTT ACT GCA	31 5
Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala	
	•
TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG	363
Leu Cys Cln Lys Leu Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp	
65 70 75	
	•
TTA ACT TGG GAG AAA GTT TGA TGT GTG GAT GGA GTA TTG GGA GGT TAT	411
Leu Thr Trp Glu Lys Val Ser Ser Val Asp Gly Val Leu Gly Gly Tyr	•:
ATT CAA AAG AAA AAG GAA CTG TGG GGA ATC TGT ATC TTT ATT GCA GCA	459
Ile Cln Lys Lys Clu Leu Trp Cly Ile Cys Ile Phe Ile Ala Ala	
95100105	
CTT GAC CTA GAT GAG ATG TCG TTC ACT TTT ACT GAG CTA CAG AAA AAC	507
Val Asp Leu Asp Glu Met Ser Phe Thr Phe Thr Glu Leu Gln Lys Asn	
	
ATA GAA ATC AGT GTC CAT AAA TTC TTT AAC TTA CTA AAA GAA ATT GAT	555
Ile Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp	
- 125 - 130 - 135	

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ACC AGT ACC AAA GTT GAT AAT GCT ATG TCA AGA CTG TTG AAG AAG TAT Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr 140 145 150	603
GAT GTA TTG TTT GCA CTC TTC AGC AAA TTG GAA AGG ACA TGT GAA CTT Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu 160 165 170	651
ATA TAT TTG ACA CAA CCC AGC AGT TCG ATA TCT ACT GAA ATA AAT TCT Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser	6.9 9
GCA TTG GTG CTA AAA GTT TCT TGG ATC ACA TTT TTA TTA GCT AAA GGG Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly 190 195 200	747
GAA GTA TTA CAA ATG GAA GAT GAT CTG GTG ATT TCA TTT CAG TTA ATG Clu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met 205 210 215	795
CTA TGT GTC CTT GAC TAT TTT ATT AAA CTC TCA CCT CCC ATG TTG CTC Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu 225 235	
AAA CAA CCA TAT AAA ACA CCT GTT ATA CCC ATT AAT CGT TCA CCT CGA Lys Clu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg 240 245	89 1
ACA CCC ACG CGA GGT CAG AAC ACG ACT GCA CGG ATA GCA AAA CAA CTA Thr Pro Arg Arg Gly Gln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu 255 260 265	939
GAA AAT GAT ACA AGA ATT ATT GAA GTT CTC TGT AAA GAA CAT GAA TGT Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys 270 275	987
AAT ATA GAT GAG GTG AAA AAT GTT TAT TTC AAA AAT TTT ATA CCT TTT Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe 285 290 295	
ATG AAT TCT CTT GGA CTT GTA ACA TCT AAT GGA CTT CCA GAG GTT GAA Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu 300 305 310	1083
AAT CTT TCT AAA CGA TAC GAA GAA ATT TAT CTT AAA AAT AAA GAT CTA Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu 320 325	
GAT GCA AGA TTA TTT TTG GAT CAT GAT AAA ACT CTT CAG ACT GAT TCT Asp Ala Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser 335 340 345	1179

•		
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Page 28	•	•
ATA GAC AGT TTT GAA ACA CAG AGA ACA CCA CGA	AAA AGT AAC CTT GAT	-1227
Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg	Lys Ser Asn Leu Asp	
CAA CAG CTC AAT GTA ATT CCT CCA CAC ACT CCA	GTT ACC ACT GTT ATC	1275
Glu Glu Val Asn Val Ile Pro Pro His Thr Pro 365 370	Val Arg Thr Val Met	
AAC ACT ATC CAA CAA TTA ATG ATG ATT TTA AAT	TCA CCA AGT GAT CAA	- 1323 .
Agn Thr Ile Gln Gln Leu Met Met Ile Leu Asn	Ser Ala Ser Asp Gln	
380 385 390	· · · · · · · · · · · · · · · · · · ·	
CCT TCA GAA AAT CTG ATT TCC TAT TTT AAC AAC	TGC ACA GTG AAT CCA	- 1371
Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn 400 405	Cys Thr Val Ash Pro	
AAA GAA ACT ATA CTG AAA AGA GTG AAG GAT ATA	CCA TAC ATC TTT AAA	1419
Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile	Gly Tyr Ile Phe Lys	
GAG AAA TTT GCT AAA GCT GTG GGA CAG GGT TGT	GTC GAA ATT GGA TCA	— 1467
Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys 430 435	—— 440	
CAG CGA TAC AAA CTT GGA GTT CGC TTG TAT TAC	CGA GTA ATG GAA TCC	1515
Gln Arg Tyr Lys Leu Cly Val Arg Leu Tyr Tyr	Arg Val Met Glu Ser	
450	455	•
ATG CTT AAA TCA GAA GAA GAA CGA TTA TCC ATT	r caa aat ttt acc aaa	— 1563
Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile 460 465 470	Gln Asn Phe Ser Lys	
CTT CTG AAT GAC AAC ATT TTT CAT ATG TCT TTA	TTG CCG TGC CCT CTT	- 1611
Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu 480 485	<u>-Leu Ala Сув Аla Беа</u>	
	•	- 1659
GAG GTT GTA ATG GCC ACA TAT AGC AGA AGT ACA Glu Val Val Met Ala Thr Tyr Ser Arg Ser Thr	Ser Gln Asn Leu Asp	1033
495 -500	505	•
TCT CGA ACA GAT TTG TCT TTC CCA TGG ATT CTG	AAT CTC CTT AAT TTA	1707
Ser Cly Thr Asp Leu Ser Phe Pro Trp Ile Leu	Asn Val Leu Asn Leu	
510 515	520	
AAA GCC TTT GAT TTT TAC AAA GTG ATC GAA AGT	TTT ATC AAA GCA GAA	1755
Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser	Phe Ile Lys Ala Glu	
		- 1803
GGC AAC TTG ACA AGA GAA ATG ATA AAA CAT TTA	Clu Arg Cys Glu His	4000
540	<u> </u>	

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CGA ATC ATG GAA TCC CTT GCA TCG CTC TCA GAT TCA CCT TTA TTT GAT Arg Ile Met Glu Ser Leu Ala Trp Leu Ser Asp Ser Pro Leu Phe Asp 560 565 570	. 1851
CTT ATT AAA CAA TCA AAG GAC CGA GAA GGA CCA ACT GAT CAC CTT GAA Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu 575 580 585	1899
TCT GCT TGT CCT CTT AAT CTT CCT CTC CAG AAT AAT CAC ACT GCA GCA Ser Ala Cys Pro Leu Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala 590 595 600	1947
CAT ATC TAT CTT TCT CCT GTA AGA TCT CCA AAG AAA AAA GGT TCA ACT Asp Met Tyr Leu Ser Pro Val Arg Ser Pro Lys Lys Cly Ser Thr 605 610	1995
ACG CGT GTA AAT TCT ACT GCA AAT GCA GAG ACA CAA GCA ACC TCA GCC Thr Arg Val Asn Ser Thr Ala Asn Ala Glu Thr Gln Ala Thr Ser Ala 620 635	2043
TTC-CAG ACC CAG AAG CCA TTG AAA TCT ACC TCT CTT TCA CTG TTT TAT Phe Gln Thr Gln Lys Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe Tyr 640 645	2091
AAA AAA GTG TAT CCC CTA GCC TAT CTC CCC CTA AAT ACA CTT TGT GAA Lys Lys Val Tyr Arg Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu 655 660 665	2139
CGC CTT CTG TCT GAG CAC CCA GAA TTA GAA CAT ATC ATC TGG ACC CTT Arg Leu Leu Ser Glu His Pro Glu Leu Glu His Ile Ile Trp Thr Leu 670 675 680	2187
TTC CAG CAC ACC CTG CAG AAT GAG TAT GAA CTC ATG AGA GAC AGG CAT Phe Gln His Thr Leu Gln Asn Glu Tyr Glu Leu Met Arg Asp Arg His 685 690	- 2235
TTG GAC CAA ATT ATG ATG TGT TCC ATG TAT GGC ATA TGC AAA GTG AAG Leu Asp Gln Ile Met Met Cys Ser Met Tyr Gly Ile Cys Lys Val Lys 700 715	2283
AAT ATA GAC CTT AAA TTC AAA ATC ATT GTA ACA GCA TAC AAG GAT CTT Asn Ile Asp Leu Lys Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu 720 730	2331
CCT CAT GCT GTT CAG GAG ACA TTC AAA CGT GTT TTG ATC AAA GAA GAG Pro His Ala Val Glu Glu Thr Phe Lys Arg Val Leu Ile Lys Glu Glu	- 2379
GAG TAT GAT TCT ATT ATA GTA TTC TAT AAC TCG GTC TTC ATG CAG AGA Glu Tyr Asp Ser Ile Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg 750 755	. 2427

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CTG AAA ACA AAT ATT TTG CAG TAT GCT TCC ACC AGG CCC CCT ACC TTG	2475
Leu Lys Thr Asn-Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu	
	
TCA CCA ATA CCT CAC ATT CCT CGA AGC CCT TAC AAG TTT CCT AGT TCA	2523
Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser	
780 795 795 795 795 795 795 795 795 795 795	
CCC TTA CCC ATT CCT GGA GGG AAC ATC TAT ATT TCA CCC CTC AAG AGT	2571
Pro Leu Arg Ile Pro Cly Cly Asn Ile Tyr Ile Ser Pro Leu Lys Ser	
<u>800</u>	
CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA	2619
Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro	
815825	
AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG	2667
Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu	
830 835 840	
AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC	2715
Lys Phe Cln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu	
845 850 850 855	
AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA	2763
Lys Arg Ser Ala Clu Cly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu	
860 865 875	
CCC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC	2811
Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu	
880 885 890	٠.
CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT	2859
Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr	•
895 900 905	
CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA	2907
Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser	
<u>910</u> 915 920	,
AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT	2962
Asn Lys Glu Glu Lys	·
925	
GGATTCATTG TCTCTCACAG ATGTGACTGT AT	2994

41. (Original) A method of therapeutically treating inactive, mutative or absent cancer suppressing genes comprising:

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treating said inactive, mutative or absent cancer suppressing genes with at least a portion of intact cancer suppressing genes.

- 42. (Original) A method of claim 41, wherein said cancer suppressing genes are each a substance selected from the groups consisting of RB genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, and mixtures thereof.
- 43. (Original) A method of claim 41, wherein said treating includes: treating said inactive, mutative or absent cancer suppressing gene with a substance selected from the group consisting of an RB gene, a portion of said gene, or a mixture thereof.
- 44. (Original) A method of claim 43, wherein said portion is selected from the group consisting of RB cDNA, RB cDNA fragment, homologues thereof and mixtures thereof.
- 45. (Original) The method of claim 41, wherein the intact cancer suppressing gene, or portion thereof, is delivered to the site of a tumor by means of a retrovirus.
- 46. (Original) A method of claim 41, wherein the intact cancer suppressing gene, or a portion thereof, is delivered to the site of a tumor by a liposome.
- 47. (Original) A method of claim 41, wherein the location of said cancer suppressing gene is determined by utilizing a genetic marker.

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47. (Previously added) A method of suppressing the neoplastic phenotype of a cancer cell, the method comprising contacting the cell with a nucleic acid encoding a full length, wild type retinoblastoma protein.

REMARKS

The amendments to the nucleotide sequence in "TABLE 4" and claims 35 and 40 correct errors of a typographical nature made without deceptive intent. The codons at nucleotide positions 223-225 (CCT), encoding "Pro", and 226-228 (GAG), encoding "Glu", were present in the original sequence from informal Figure 9 of the parent application, 08/472,760, filed November 27,1996, a copy of which is enclosed for the convenience of the Examiner. These codons were inadvertently changed to "CCG" and "TAG" in the present application. That this is inadvertent error is supported by the fact that, under "TAG" at positions 226-228, which encodes a stop codon, the originally-encoded amino acid "E" (Glu) appears in "TABLE 4" of the Specification submitted on December 21, 2001, and "Glu" again appears in the Substitute Specification submitted April 30, 2002, in response to the Notice to File Corrected Application Papers, mailed January 31, 2002.

The Sequence Listing submitted for Application No. 08/472,760, filed November 27,1996, does not contain these inadvertent errors and, thus, the amendments to the Specification and Claims now seek to conform to the nucleotide sequence present in the Sequence Listing of the parent application.

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. The information contained in the computer readable form of Application No. 08/472,760 was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy, a copy of which is enclosed for the convenience of the Examiner. This amendment contains no new matter.